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Medical Progress

The Differential Diagnosis of Pleural Effusions

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The presence of pleural effusion enables a physician to obtain a specimen of a body cavity fluid easily. With a systematic analysis of the pleural fluid, in conjunction with the clinical features and ancillary laboratory data, a clinician should be able to arrive at either a presumptive or definitive diagnosis in approximately 90 percent of cases. Selectivity should be exercised in ordering analyses on pleural fluid. The first important deductive step is to decide whether the effusion is a transudate (due to imbalances in hydrostatic or oncotic pressures) or an exudate (inflammatory); serum protein and lactate dehydrogenase measurements will be decisive. The differential diagnosis of a transudate is relatively limited and usually easily discernible from the clinical presentation. The differential diagnosis of exudate poses a more difficult challenge for clinicians. The use of certain pleural fluid tests such as leukocyte count and differential, glucose, pH and, when indicated, pleural fluid amylase determinations, helps to narrow the differential diagnosis of an exudative pleural effusion.

CLINICIANS FREQUENTLY are confronted with patients with pleural effusions. The presence of this pleural fluid provides the simple opportunity to get a specimen of a body cavity fluid to support the clinical impression. Knowledge of the physiology of pleural fluid formation and analysis of the cellular content and chemistry of these effusions, in conjunction with the history, physical examination and ancillary laboratory data, should enable a clinician to reach a presumptive or definitive diagnosis in about 90 percent of patients with pleural effusions. Pleural fluid analysis is similar to other laboratory tests in medicine; these tests rarely provide a definitive diagnosis but support the clinical impression. The only pleural fluid findings that provide a definitive diagnosis are (1) the presence of malignant cells, (2) a positive Gram stain, acid-fast bacilli (AFB) stain or pleural fluid culture and (3) the presence of lupus erythematosus (LE) cells.

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Physiology of Pleural Fluid Formation

The passage of pleural fluid across the pleural membrane in normal humans is dependent on the opposing hydrostatic and oncotic pressures acting on both the visceral and parietal pleural membranes.[1,2] Normally, the oncotic pressures on both

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
LDH = lactate dehydrogenase
LE = lupus erythematosus
Pa_{O_2} = arterial oxygen partial pressure (tension)

sides of the parietal and visceral pleura are equal; thus, the difference in forces is attributable to the inequality in hydrostatic pressures between the systemic circulation that supplies the parietal pleura and the lower pressure pulmonary circulation that supplies the visceral pleura. The magnitude of these forces suggests that fluid is formed at the parietal pleural surface and absorbed by the visceral pleural capillaries in a dynamic state. Protein and red blood cells, however, are absorbed only by the lymphatic vessels draining the pleural space.[3] Despite these forces, a thin layer of liquid remains in the pleural space in the normal state; this alkaline fluid contains less than 2 grams per dl of protein and a low number of mononuclear cells.[4,5]

Conditions Under Which Abnormal Amounts of Pleural Fluid Develop

Abnormal amounts of pleural fluid accumulate when there is an increase in hydrostatic pressure (congestive heart failure), a decrease in colloid osmotic pressure (severe hypoalbuminemia), an increase in capillary permeability (pneumonia), increased intrapleural negative pressure (atelectasis) and decreased lymphatic drainage (mediastinal carcinomatosis). Blood may enter the pleural space because of trauma (blunt injury, thoracentesis, tumor erosion of a vessel), and chyle may accumulate from rupture of the thoracic duct and disruption of the mediastinal parietal pleura.

Clinical Features of Pleural Effusions

The symptoms that cause a patient to seek medical attention usually are not due to the presence of the effusion itself but to the underlying disease process. However, a large effusion may cause dyspnea at rest in patients with underlying lung disease or dyspnea on exertion in patients with normal lungs.

When a pleural effusion develops the lung is separated from the chest wall by a layer of fluid that interferes with sound transmission. The physical findings with a pleural effusion will vary depending on the size of the effusion, involvement of the underlying lung and the degree of lung compression. Physical findings with varying degrees of pleural fluid are summarized in Table 1.

There are important points to remember about physical findings with a pleural effusion:

- Physical findings may be normal when there is less than 300 ml of fluid in the pleural space.
- It generally takes more than 1,000 ml of pleural fluid to cause a contralateral mediastinal shift.
- When a contralateral mediastinal shift does not occur with the critical or apparent critical volume of fluid, the following four diagnoses should be considered: (1) carcinoma of the mainstem bronchus with atelectasis of the ipsilateral lung, (2) a fixed mediastinum due to neoplastic lymph nodes, (3) malignant mesothelioma and (4) pronounced infiltration of the ipsilateral lung, usually with tumor.

Appearance of Pleural Fluid on Chest Roentgenogram

Free pleural fluid has a characteristic appearance on an upright chest roentgenogram in the absence of pleural disease. It produces a homogeneous density through which lung markings may be discerned. The upper margin of the fluid forms a meniscus (concave upward) at the lateral chest wall. Small effusions may reveal only blunting of the costophrenic angle or may be seen as a "thickening" of either the minor fissure on the posteroanterior view or the minor and major fissures on the lateral view. A critical amount of fluid (probably 200 ml) needs to be present in an adult to be detectable on an upright chest roentgenogram. A lateral decubitus view, however, will show lesser amounts of free fluid. Occasionally fluid will be situated between the bottom of the lung and the diaphragm (subpulmonic effusion). Subpulmonic effusion can be confirmed with a lateral decubitus view. Fluid may loculate in the pleural space, including the intralobar fissures, and may produce a "pseudotumor."

Indications for Thoracentesis

Diagnostic

When a pleural effusion is recognized, a diagnostic thoracentesis should be done either to support the clinical impression or for further diagnostic information when the clinical situation is unclear. Exceptions to this rule might be when the clinical diagnosis is secure and only a small amount of pleural fluid is present—that is, when

TABLE 1.—*Physical Signs of Pleural Effusion*

Amount of Effusion	*Expansion*	*Fremitus*	*Percussion*	*Breath Sounds*	*Contralateral Mediastinal Shift*
1. Small effusion ..	N	N	N	v	0
2. 300-1,000 ml ...	↓	↓	f	↓v	0
3. 1,000-2,000 ml ..	↓↓	↓	f	↓↓bv	+
4. >2,000 ml	↓↓↓	↓↓	f	↓↓↓−0	++

N = normal; ↓ = decrease; f = flat; v = vesicular; bv = bronchovesicular; 0 = absent; + = present.

the benefit-to-risk ratio is small—or in a patient with uncomplicated congestive heart failure (afebrile, a compatible clinical history and arterial oxygen tension (Pao_2) not out of proportion to the clinical situation). In the above situations, continued observation without thoracentesis may be warranted. However, a clinician should not hesitate to do a thoracentesis if the situation changes.

Therapeutic

When a patient with a large effusion, usually due to malignancy, is dyspneic because of the effusion, a therapeutic thoracentesis should be carried out. The dyspnea in these instances probably is related more to neurogenic factors in compressed lung tissue than to oxygen chemosensors, as most patients have a relief of dyspnea following thoracentesis even if the Pao_2 falls.[6,7] Not more than 1,000 ml of pleural fluid should be removed at one sitting without monitoring pleural fluid pressure.[8]

Complications of Thoracentesis

Complications of thoracentesis include pneumothorax, hemorrhage (hematoma, intrapleural,[9] intra-abdominal[10]), empyema, pain, hypoxemia, liver or spleen[11] puncture and unilateral pulmonary edema.[12] Pneumothorax can be avoided by inserting the needle one interspace below the level where the physical findings change. One should do the thoracentesis at the highest interspace dictated by physical examination; this will avoid spleen or liver puncture. Oxygen by nasal cannula should be administered during and for 24 hours after a therapeutic thoracentesis to prevent the fall of Pao_2 that commonly occurs.[6,7]

Pleural Fluid Analysis

When the thoracentesis is done, the fluid should be analyzed in a systematic manner. Color, odor and character of the fluid should be noted. The following laboratory tests are commonly carried out on pleural fluid: leukocyte count and differential, erythrocyte count, total protein, glucose, lactate dehydrogenase (LDH), amylase and pH determinations; Wright, Gram and AFB stains; aerobic, anaerobic, tuberculosis and fungal cultures; and cytology. *All* of these tests do not need to be done on all fluids. The expense is exorbitant and the diagnostic usefulness of the entire battery is small. A clinician should select the appropriate tests depending on the clinical situation. For example, a pleural fluid amylase level should be ordered only when pancreatitis, pancreatic pseudocyst or esophageal rupture is suspected.

Observation

All transudative fluids and some exudates are clear and straw colored. Other hints from observation include a milky color that suggests chylothorax, a reddish tinge indicating blood and an anchovy color that occurs when an amebic liver abscess has ruptured into the pleural space. Both a large number of leukocytes and increased lipids will make the pleural fluid appear turbid. A simple bedside test for differentiating elevated leukocyte counts from lipids is to centrifuge the fluid; if the supernatant clears, the turbidity is due to leukocytes. With chylothorax, chylomicrons produce a whitish layer on top of the centrifuged fluid. Pus aspirated from the pleural space establishes a diagnosis of empyema. Anaerobic empyemas have a characteristic putrid color in 50 percent to 60 percent of cases. A very viscous fluid that is hemorrhagic suggests a malignant mesothelioma.

Leukocytes

If the leukocyte count is more than 1,000 per μl, the fluid is likely an exudate. Conversely, leukocyte counts less than 1,000 per μl suggest that a fluid is a transudate.[13] Neutrophils predominate early in inflammatory effusions due to pneumonia, pulmonary infarction, pancreatitis, tuberculosis or lupus. Several days after the acute

insult to the pleura, mononuclear cells predominate in the effusion. Pleural macrophages appear early and are followed by lymphocytes.[14] Mononuclear cells predominate in transudative pleural effusions and chronic exudative effusions[15] (caused by, for example, tuberculosis, lymphoma, carcinoma, uremic pleurisy or rheumatoid pleurisy). The reason that these exudative effusions are mononuclear predominant is that patients with these diseases usually are not seen in the acute phase; by the time a thoracentesis is done the acute inflammatory process has subsided and the polymorphonuclear leukocyte predominance has changed to a mononuclear predominance.

Finding pleural fluid eosinophilia (more than 10 percent of total leukocytes) does not provide a specific diagnosis but offers certain useful information. These effusions are exudates with a large population of lymphocytes and tend to be self-limiting and with a favorable outcome.[16] The presence of the eosinophils makes the diagnosis of tuberculosis unlikely.[13,17] Eosinophils frequently are found when blood or air has entered the pleural space and thus may be noted with a pneumothorax or hemothorax. Pleural fluid eosinophilia also may be found with pulmonary infarction, polyarteritis nodosa and parasitic and fungal disease.[17]

Erythrocytes

The presence of 5,000 to 10,000 erythrocytes per μl will cause fluid to appear hemorrhagic. When pleural fluid is grossly hemorrhagic in the absence of trauma, malignancy must be considered. When the erythrocyte count is more than 100,000 per μl, the diagnosis is usually a malignant lesion or trauma or, less likely, pulmonary infarction.[13,18] Transudative effusions are rarely sanguineous and the finding of a bloody effusion in the setting of congestive heart failure should raise the possibility of a concomitant pulmonary infarction, though 10 percent of pleural effusions due to congestive heart failure alone may be serosanguineous.[19] Tuberculous pleural effusions are usually serous or serosanguineous (less than 10 percent) and rarely grossly bloody. There are two bedside tests that can be used to determine whether the thoracentesis is traumatic or the fluid is actually bloody: (1) Measure the hematocrit of the fluid and compare it with the blood hematocrit. Identical hematocrit ranges usually indicate traumatic thoracentesis, but this finding can be seen with chest trauma and, rarely, malignancy. (2) Note whether the pleural fluid clots. A traumatic thoracentesis fluid should clot within several minutes, whereas pleural fluid that has been present for several hours to days will become defibrinated and will not form a good clot.

Glucose

A normal pleural fluid glucose value (more than 60 mg per dl, or a pleural fluid-to-serum ratio of over 0.5) is not particularly helpful; however, a low pleural fluid glucose level (less than 60 mg per dl or a pleural fluid-to-serum ratio of under 0.5) will help narrow the differential diagnosis of the exudative pleural effusion. The following diagnoses have been associated with a low pleural fluid glucose level: (1) rheumatoid pleurisy—usually less than 30 mg per dl[20]; (2) empyema—glucose level almost always low and ranges between 0 and 60 mg per dl[21,22]; (3) carcinoma—glucose concentration decreased in approximately a third of patients, especially those with chronic effusions, usually between 20 and 60 mg per dl[23,24]; (4) tuberculosis—probably less than 20 percent of cases in which the level is usually between 30 and 60 mg per dl; (5) esophageal rupture—glucose almost always low due to anaerobic empyema[25]; (6) lupus pleuritis—incidence not known, but decreased glucose concentration is usually transient.[26]

The mechanisms responsible for a low pleural fluid glucose level appear to be a combination of enhanced glycolysis by either pleural fluid cells, bacteria or pleural tissue in conjunction with an impairment to transport of glucose from blood to pleural fluid.[22,24,27,28] For the most accurate interpretation of pleural fluid glucose level, thoracentesis should be carried out while a patient is in a fasting state and a serum glucose determination obtained at the same time. When pleural fluid is collected for glucose analysis, fluid must either be frozen or stored with a substance such as sodium fluoride that prevents in vitro glycolysis.

Total Protein and LDH, Transudates vs Exudates

In determining the differential diagnosis of a pleural effusion, it is important to classify the fluid as either a transudate or an exudate. The differential diagnosis of transudate is limited and the clinical diagnosis usually is apparent from the history and physical examination. Exudative pleural effusions have many more diagnostic possibilities and occur most commonly when there is an inflammatory process involving the pleura. When

inflammation affects the pleura, proteins leak from the pleural capillaries into the pleural space; thus, it would be expected that total protein and LDH levels would increase. If any one of the three following criteria is present, the fluid is usually an exudate: (1) a pleural fluid to serum protein ratio of over 0.5, (2) a pleural fluid LDH level of more than 200 IU and (3) a pleural fluid-to-serum LDH ratio of over 0.6.[29] The various sources of transudates and exudates are shown in Table 2.

Amylase

An elevated pleural fluid amylase value (over 160 Somogyi units per dl), or at least twice the serum amylase value suggests one of the four following diagnoses: acute pancreatitis[30,31]; pancreatic pseudocyst[30,31]; esophageal rupture,[32] and, rarely, primary or metastatic carcinoma of the lung.[33] An increased concentration of pleural fluid amylase (500-2,000 Somogyi units per dl) probably results from lymphatic passage or seepage of the enzyme across the diaphragm or by direct transdiaphragmatic communication (in the case of more than 20,000 Somogyi units per dl) between the pleural space and abdominal cavity. An additional hypothesis is that leakage of the enzyme from blood to pleural space reflects impaired reabsorption due to a damaged pleural surface.

TABLE 2.—*Causes of Pleural Effusions*

Transudates
Congestive heart failure
Cirrhosis with ascites
Nephrotic syndrome
Hypoalbuminemia
Peritoneal dialysis
Atelectasis, acute
Superior vena cava obstruction
Subclavian catheter misplacement
Early mediastinal malignancy
Exudates
Parapneumonic effusion (bacterial pneumonia)
Pulmonary infarction
Malignancy (direct pleural involvement, late mediastinal involvement)
Viral disease
Connective tissue disease (lupus, rheumatoid, mixed)
Tuberculosis
Fungal disease
Parasitic disease *(Entamoeba histolytica, Paragonimus westermani)*
Gastrointestinal disease (pancreatitis, esophageal rupture, subphrenic abscess)
Drug reaction (nitrofurantoin, methysergide)
Asbestos
Meigs' syndrome
Postmyocardial infarction and postcardiac surgical operation
Trapped lung
Lymphatic abnormality
Uremic pleurisy
Atelectasis, chronic
Chylothorax
Sarcoidosis

Lipids

Chylous effusions (chylothorax) occur when the contents of the thoracic duct empty into the pleural space. The most common cause is malignancy, usually lymphoma, which causes a rupture of the thoracic duct, drainage into the mediastinum and then extension into the pleural space.[34] Other causes of a chylothorax are surgical procedures and trauma. These chylous effusions contain chylomicrons and a high level of triglycerides.[35] If a thoracentesis is done within a few hours of a meal, chylomicrons can be seen as the top whitish layer in a centrifuged specimen. In general, triglyceride levels will be more than twice the concentration of that in a simultaneous serum specimen. These fluids also will stain positive with Sudan III.

Chyliform effusions are long-standing effusions seen in tuberculous pleurisy, trapped lung* or rheumatoid pleurisy and are characterized by high concentrations of cholesterol, low levels of triglycerides and no chylomicrons; they do not stain positive with Sudan III.[36] The high concentration of cholesterol is due to cellular degeneration.

pH

The finding of a low pleural fluid pH (less than 7.30) provides a clinician with the following information: (1) The fluid is always an exudate; (2) the differential diagnosis of the exudate is narrowed to empyema, malignancy, rheumatoid pleurisy, lupus pleuritis, tuberculosis and esophageal rupture[37]; (3) a parapneumonic effusion is either an empyema or will behave clinically like an empyema and usually requires chest tube drainage,[38] and (4) the finding has diagnostic, prognostic and therapeutic implications in malignant effusions.[39] Pleural fluid pH should be obtained as an arterial blood gas in a heparinized syringe and maintained anaerobically on ice until analyzed.

Cytology

About 25 to 50 ml of pleural fluid is all that is required for adequate cytologic examination. A small amount of heparin should be added to the

*A trapped lung results from infection in the pleural space when a fibrous "peel" encases the lung and does not permit expansion to the chest wall.

specimen to inhibit clotting, which could cause cellular distortion. The specimen should be brought to the laboratory immediately for processing; if this is impossible, the fluid should be kept refrigerated until it can be taken to the laboratory. In cases of proved carcinoma of the pleura, cytology is positive in approximately 50 percent to 70 percent of patients.[40-42] Some of the false-negative cytology findings may be due to improper handling of specimens, a long-standing effusion with many degenerative cells or a lack of interest or expertise in the pathology laboratory. Pleural effusions associated with malignancy may not be due to carcinomatous involvement of the pleura but to lymphatic obstruction, endobronchial obstruction with pneumonia or endobronchial obstruction with atelectasis. Characteristics that suggest malignancy include cells that have large nuclei, a high nucleocytoplasmic ratio and clumping. If the first pleural fluid specimen is negative and carcinoma is suspected, another specimen of fluid should be obtained that would yield fresher cells and a lower percentage of degenerative mesothelial cells. The yield of repeat cytology in carcinoma of the pleura is 17 percent to 22 percent.[42,43]

Staining of Pleural Fluid

A Wright's stain of centrifuged pleural fluid will enable better differentiation of neutrophils from mononuclear cells, will aid in the identification of eosinophils and will enable the identification of LE cells pathognomonic of lupus pleuritis. Differentiation of the types of mononuclear cells is not reliable with Wright's stain and requires special staining techniques. A Gram stain of centrifuged pleural fluid should be obtained routinely in an attempt to establish the diagnosis of pleural space infection. Smears of pleural fluid for AFB are positive in approximately 20 percent to 30 percent of patients with tuberculous pleurisy.[44]

Indication for Pleural Biopsy

A pleural biopsy with a Cope's or Abrams' needle should be done where there is an undiagnosed exudative pleural effusion. Usually it is diagnostic only when there is a mononuclear-predominant exudate such as found in tuberculosis, carcinoma and lymphoma. Carcinoma may be diagnosed on pleural biopsy in approximately 60 percent of cases of carcinoma of the pleura.[42] The yield probably can be increased if the operator takes three to five biopsy specimens from two separate sites. Closed pleural biopsy in tuberculous pleurisy will be positive in 70 percent to 85 percent of patients either by tissue histology or culture of the tissue specimens.[45]

Common Causes of Pleural Effusions

Congestive Heart Failure

Pleural effusions (see Table 3) occur in congestive heart failure when there is combined right- and left-sided heart failure, that is, both systemic and pulmonary venous hypertension. Thus, a patient will have distended neck veins, positive hepatojugular reflux, edema, rales and a left ventricular gallop. The effusions of congestive heart failure usually are bilateral but can be unilateral and have been found to occur in the left side only in up to 20 percent of cases.[46,47] This transudative effusion is clear and straw colored and generally contains less than 1,000 cells per μl. The cells are predominantly lymphocytes and mesothelial cells.[48] The protein concentration is usually less than 3 grams per dl but occasionally will increase to higher levels or have a pleural fluid-to-serum ratio of over 0.5 in chronic congestive heart failure treated with diuretics.[49]

Cirrhosis of the Liver

Pleural effusions will develop in approximately 5 percent of patients with cirrhosis and clinically demonstrable ascites.[50] The effusions are usually right sided but may be bilateral or isolated to the left side. The fluid probably moves from the peritoneal to pleural cavity via defects in the diaphragm or via diaphragmatic lymphatic channels. The fluid is a transudate with cell counts generally less than 500 per μl, with the cells predominantly mononuclear. The characteristics of the pleural and peritoneal fluid are similar, though the pleural fluid has a slightly higher protein concentration.

Parapneumonic Effusions and Empyemas

A parapneumonic effusion is any pleural effusion associated with a bacterial pneumonia or lung abscess. The fluid may be clear or turbid and sterile and resolve without sequelae (uncomplicated parapneumonic) with antibiotic treatment directed at the pneumonia. Or the fluid may be frankly purulent and loculate in the pleural space (empyema or complicated parapneumonic). Parapneumonic effusions commonly occur following bacterial pneumonias. They have been found in

TABLE 3.—*Pleural Fluid Characteristics in Common Diseases**

Diagnosis	*Appearance*	*Total Leukocytes (per μl)*	*Predominant Leukocytes*	*RBC (per μl)*	*Protein*	*Glucose*	*LDH*	*Amylase*	*pH*	*Comment*
Transudates										
Congestive heart failure	Clear, straw-colored	<1,000	M	0-1,000	PF/S<0.5	PF=S	PF/S<0.6 <200 IU/L	≤S	>7.40	Usually presence of biventricular failure
Cirrhosis	Clear, straw-colored	<500	M	<1,000	PF/S<0.5	PF=S	PF/S<0.6 <200 IU/L	≤S	>7.40	Incidence 5% of cirrhotic patients with ascites
Exudates										
Parapneumonic (uncomplicated)	Turbid	5,000-25,000	P	<5,000	PF/S>0.5	PF=S	PF/S>0.6	≤S	>7.30	Resolves with antibiotics only
Empyema	Turbid to purulent	25,000-100,000	P	<5,000	PF/S>0.5	0-60 mg/dl PF/S<0.5	PF/S>0.6 some >1,000 IU/L	≤S	<7.30	Requires tube drainage
Pulmonary infarction	Straw-colored to bloody	5,000-15,000	P	1,000-100,000	PF/S>0.5	PF=S	PF/S>0.6	≤S	>7.30	Small effusion with basal alveolar infiltrate and elevated diaphragm
Tuberculosis	Straw-colored to serosanguineous	5,000-10,000	M	<10,000	PF/S>0.5	PF=S or <60 mg/dl	PF/S>0.6	≤S	<or>7.30	Positive PPD, AFB stain and culture of pleural tissue often diagnostic
Rheumatoid disease	Turbid, green to yellow	1,000-20,000	M or P	<1,000	PF/S>0.5	<30 mg/dl	Often >1,000 IU/L	≤S	<7.30	Men, rheumatoid nodules, low pleural fluid complement
Carcinoma	Turbid to bloody	<10,000	M	1,000 to several 100,000	PF/S>0.5	PF=S or <60 mg/dl	PF/S>0.6	≤S	<or>7.30	Cytology and pleural biopsy enable diagnosis in 80%
Pancreatitis	Turbid	5,000-20,000	P	1,000-10,00	PF/S>0.5	PF=S	PF/S>0.6	PF/S>2	>7.30	Occurs in 6% of cases of pancreatitis: left sided in 70%

RBC=red blood cells; LDH=lactate dehydrogenase; M=mononuclear; PF=pleural fluid; S=serum; P=polymorphonuclear; PPD=tuberculin skin test with purified protein derivative; AFB=acid-fast bacilli.

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approximately 60 percent of patients after *Streptococcus pneumoniae* pneumonia[51] and in close to 50 percent of patients with all forms of bacterial pneumonia.[52] Pleural effusions with viral pneumonia and *Mycoplasma pneumoniae* pneumonia occur in about 20 percent of patients; these effusions are small and usually can only be seen by a lateral decubitus view on x-ray study.[53] The exact incidence of pleural effusions in Legionnaires' disease is unknown, but it probably falls somewhere between that of viral and bacterial pneumonias.

Uncomplicated parapneumonic effusions are exudates with leukocyte counts ranging generally from 5,000 to 25,000 per μl. They are neutrophil predominant with high protein concentrations, normal glucose levels and a pH of over 7.30. With antibiotic therapy alone, these effusions resolve over a few days without pleural space loculation.[38] Empyema is diagnosed by aspirating purulent fluid from the pleural space. However, certain nonpurulent pleural effusions have either a positive Gram stain, positive culture or a low pleural fluid pH (complicated parapneumonic effusion), behave like an empyema and form loculations in the pleural space.[38] With empyemas there will generally be leukocyte counts of more than 50,000 per μl (though counts can be extremely low), a low pleural fluid glucose level (0 to 60 mg per dl) and a low pleural fluid pH (less than 7.30). The most common organisms responsible for empyemas today are anaerobic organisms, *Staphylococcus aureus* and Gram-negative aerobic bacilli.[54]

Empyema should be suspected in the presence of pneumonia when a patient continues to be febrile despite antibiotic therapy and in whom a pleural effusion or increasing amounts of pleural fluid develop. A diagnostic thoracentesis should be done immediately in the latter two situations and when fluid is observed on radiograph in the first instance.

The treatment of empyema consists of immediate and complete drainage of the pleural space by chest tube and administration of appropriate antimicrobial agents selected on the basis of aerobic and anaerobic cultures. If adequate pleural space drainage cannot be accomplished by chest tube and the patient remains septic, thoracotomy needs to be done to establish effective drainage.

Pulmonary Infarction

Pleural effusions in pulmonary infarction are generally small, serosanguineous exudates that are neutrophil predominant. However, if the thoracentesis is delayed for several days following the acute injury, a mononuclear-predominant effusion may occur. Finding a bloody pleural effusion is one of the most helpful differential points between pulmonary infarction and pneumonia. The combination of diaphragmatic elevation, a basal peripheral pulmonary infiltrate and a small pleural effusion composes a radiographic triad suggestive of pulmonary infarction. In patients with pulmonary emboli without infarction a transudative effusion due to atelectasis may develop.

Carcinomatous Pleurisy

Carcinoma involving the pleura signals incurability. It represents either secondary metastasis from lung cancer or tertiary spread from a primary lesion below the diaphragm.[55] The most common primary tumors metastasizing to the pleura are of the lung, breast, stomach and ovary.[56] Carcinomatous pleurisy is almost always associated with mediastinal lymph node carcinomatosis. Impaired lymphatic drainage due to the infiltrated mediastinal lymph nodes is the primary pathogenic mechanism for accumulation of pleural fluid.[55,56] A malignant pleural effusion is usually moderate to massive in size and is frequently hemorrhagic with low leukocyte counts and a mononuclear predominance.[56] A massive bloody effusion in the absence of trauma is almost always due to malignancy.[13,57] The finding of a low glucose level and low pH in a malignant effusion suggests that the effusion has been present for several months, that the malignancy is far advanced, survival is in weeks to months and response to sclerosing agents is poor.[39,58] When both the pleural fluid cytology examination and pleural biopsy are carried out in patients with far-advanced carcinoma of the pleura, the diagnostic yield approaches 90 percent.[42]

Tuberculous Pleurisy

Tuberculous pleural effusions often occur in the absence of radiographic evidence of pulmonary tuberculosis. The formation of pleural fluid is partly a result of hypersensitivity to tuberculin protein. A tuberculous effusion is usually straw colored (serosanguineous less than 20 percent of the time), with leukocyte counts less than 10,000 per μl and a mononuclear (lymphocyte) predominance.[13,45] A neutrophil-predominant effusion may be seen in acute tuberculous pleurisy. The presence of either a large percentage of mesothe-

lial cells[59] or eosinophils[13,17] in the pleural fluid makes the diagnosis of tuberculous pleurisy unlikely. Occasionally a low pleural fluid pH and low glucose level are found. The diagnosis of a tuberculous pleural effusion depends on: (1) a positive AFB stain of pleural fluid specimen (20 percent), (2) a positive pleural fluid culture for *Mycobacterium tuberculosis* (20 percent to 70 percent), (3) the finding of a caseating granuloma in pleural tissue (25 percent to 40 percent) or (4) culturing *M tuberculosis* from pleural tissue (55 percent to 80 percent).

Rheumatoid Pleurisy

Rheumatoid pleural effusions are most commonly found in men with rheumatoid nodules, active articular disease and high serum rheumatoid factors.[60,61] However, the effusion per se may produce no symptoms and may antedate clinical evidence of arthritis.[61]

The effusion is usually unilateral and it is rare for the interstitial lung disease or necrobiotic nodules of rheumatoid lung disease to be present. The effusion characteristically is present for months or years. The pleural fluid has a yellow to yellowish-green color and usually is turbid. The leukocyte count varies from several thousand to 20,000 per μl, with the cellular predominance depending on whether the presentation is acute or chronic. The LDH concentration is generally high (frequently more than 1,000 IU per liter). The pleural fluid characteristically has a glucose concentration of less than 30 mg per dl and a pH of around 7.00.[20,37,62] The mechanism for the low glucose concentration appears to be a selective block in glucose transport from blood to pleural space[63] and glycolysis by the pleural membrane.[27] Pleural biopsy usually reveals nonspecific inflammation but occasionally a rheumatoid nodule may be seen.

Pleural Effusions Associated With Pancreatitis

The exact incidence of pleural effusions associated with acute pancreatitis is unknown but probably approaches 10 percent.[64] The effusions are small to moderate in size and are usually left sided but may be bilateral or isolated to the right side.[64] The effusion is usually a serosanguineous exudate with a polymorphonuclear predominance and with amylase levels at least twice as high as the upper limit of the serum amylase level and higher than a simultaneously determined serum amylase level.

Treatment of Pleural Effusions

The treatment of a pleural effusion should be directed at the underlying cause. In all instances, with the exception of empyema and carcinoma, this does not involve direct manipulation of the pleural space. In an empyema, adequate drainage by chest tube must be established. The failure of a good clinical response in empyema is almost never due to the inability of antibiotic action to penetrate the pleural space but to inadequate drainage.[65] If this cannot be accomplished by chest tube and the patient remains septic, a thoracotomy needs to be done so that effective drainage can be accomplished.

In patients with intractable malignant effusions leading to dyspnea, producing pleural symphysis with chest tube drainage and instillation of a sclerosing agent usually are effective palliative measures. Excellent results with minimal morbidity in properly selected patients have been achieved with tetracycline hydrochloride.[66]

REFERENCES

1. Starling EM, Tubby AH: On absorption from and secretion into the serous cavities. J Physiol (London) 1894; 16:140-155
2. Leathes JB, Starling EM: The absorption of salt solution from the pleural cavities. J Physiol (London) 1895; 18:106-116
3. Courtice FC, Simmonds WJ: Physiological significances of lymph drainage of the serous cavities and lung. Physiol Rev 1954; 34:419-448
4. Yamada S: Über die serose Flussigkeit in der Pleurahole der gesunden Menschen. Z Gesamte Exptl Med 1933; 90:342-348
5. Sahn SA, Willcox ML, Good JT Jr, et al: Characteristics of normal rabbit pleural fluid—Physiologic and biochemical implications. Lung 1979; 156:63-69
6. Karetzky MS, Kothari GA, Fourre JA, et al: Effect of thoracentesis on arterial oxygen tension. Respiration 1978; 36:96-103
7. Brandstetter RD, Cohen RP: Hypoxemia after thoracentesis: A predictable and treatable condition. JAMA 1959; 242:1060-1061
8. Light RW, Jenkinson SG, Minh VD, et al: Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis 1980 May; 121:799-804
9. Carney M, Ravin CE: Intercostal artery laceration during thoracentesis—Increased risk in elderly patients. Chest 1979; 75: 520-522
10. Heffner JE, Sahn SA: Abdominal hemorrhage after perforation of a diaphragmatic artery during thoracentesis (Letter). Arch Intern Med 1981 Aug; 141:1238
11. Braveny I, Machka K: Delayed iatrogenic rupture of the spleen. Lancet 1980 Oct 4; 2:754-755
12. Trapnell DH, Thurston JB: Unilateral pulmonary edema after pleural aspiration. Lancet 1970; 1:1367-1369
13. Light RW, Erozan YS, Ball WC Jr: Cells in pleural fluid—Their value in differential diagnosis. Arch Intern Med 1973; 132: 854-860
14. Sahn SA: Cells, proteins and the acid-base status of pleural fluid in health and disease, *In* Hirsch A, Chretien J (Eds): Diseases of the Pleura. New York, Masson Publishing, 1981
15. Yam L: Diagnostic significance of lymphocytes in pleural effusions. Ann Intern Med 1967; 66:972-982
16. Veress JF, Koss LG, Schreiber K: Eosinophilic pleural effusions. Acta Cytol (Baltimore) 1979; 23:40-44
17. Campbell GD, Webb WR: Eosinophilic pleural effusion. Am Rev Respir Dis 1964; 90:194-201
18. Bynum LJ, Wilson JB III: Characteristics of pleural effusions associated with pulmonary embolism. Arch Intern Med 1976; 136:159-162
19. Griner PF: Bloody pleural fluid following pulmonary infarction. JAMA 1967; 202:123-125
20. Carr DT, Power MH: Pleural fluid glucose with special reference to its concentration in rheumatoid pleurisy with effusion. Dis Chest 1960; 37:321-324, 1960
21. Potts DE, Taryle DA, Sahn SA: The glucose-pH relationship in parapneumonic effusions. Arch Intern Med 1978; 138:1378-1380

22. Potts DE, Willcox M, Good JT Jr, et al: The acidosis of low glucose pleural effusions. Am Rev Respir Dis 1978; 117:665-671

23. Clarkson B: Relationship between cell type, glucose concentration, and response to treatment in neoplastic effusions. Cancer 1964; 17:914-928

24. Good JT Jr, Taryle DA, Kaplan RL, et al: Pathogenesis of low glucose-low pH malignant effusions. Am Rev Respir Dis 1979; 119:119

25. Maulitz RM, Good JT Jr, Kaplan RL, et al: The pleuropulmonary consequences of esophageal rupture: An experimental model. Am Rev Respir Dis 1979; 120:363-367

26. Good JT Jr, King TE, Sahn SA: Native and drug-induced lupus pleuritis: A cause of low glucose-low pH pleural effusion. Chest 1980; 78:518

27. Taryle DA, Good JT Jr, Sahn SA: Acid generation by pleural fluid: Possible role in the determination of pleural fluid pH. J Lab Clin Med 1979 Jun; 93:1041-1046

28. Sahn SA, Good JT Jr, Reller LB: The contribution of leukocytes and bacteria to the acidosis of empyema. Clin Res 1980; 28:45A

29. Light RW, MacGregor MI, Luchsinger PC, et al: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77:507-513

30. Goldman M, Goldman G, Fleischner FG: Pleural fluid amylase in acute pancreatitis. N Engl J Med 1962; 266:715-716

31. Light RW, Ball WC Jr: Glucose and amylase in pleural effusions. JAMA 1973; 225:257-259

32. Sherr HP, Light RW, Merson MH, et al: Origin of pleural fluid amylase in esophageal rupture. Ann Intern Med 1972; 76: 985-986

33. Ende N: Studies of amylase activity in pleural effusions and ascites. Cancer 1960; 13:283-287

34. Roy PH, Carr DT, Payne WS: The problem of chylothorax. Mayo Clin Proc 1967; 42:457-467

35. Seriff NS, Cohen ML, Samuel P, et al: Chylothorax: Diagnosis by lipoprotein electrophoresis of serum and pleural fluid. Thorax 1977; 32:98-100

36. Ferguson G: Cholesterol pleural effusion in rheumatoid lung disease. Thorax 1966; 21:577-582

37. Good JT Jr, Taryle DA, Maulitz RM, et al: The diagnostic value of pleural fluid pH. Chest 1980 Jul; 78:55-59

38. Potts DE, Levin DC, Sahn SA: Pleural fluid pH in parapneumonic effusions. Chest 1976; 70:328-331

39. Good JT Jr, Taryle DA, Sahn SA: Pleural fluid pH in malignant effusions: Pathophysiologic and prognostic implications. Chest 1978; 74:338

40. Jarva OH, Kunnas RJ, Laitio MT, et al: The accuracy and significance of cytologic cancer diagnosis of pleural effusions: A follow-up of 338 patients. Acta Cytol 1972; 16:152-156

41. Lopes Cardoza P: A critical evaluation of 3,000 cytologic analyses of pleural fluid, ascitic fluid, and pericardial fluid. Acta Cytol 1966; 10:455-460

42. Salyer WA, Eggleston JC, Erozan YS: Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasm involving the pleura. Chest 1975; 67:536-539

43. Boutin C, Arnaud A, Farisse P: Les biopsies pleurales: Incidents et rentabilité acuelle de la biopsie a l'aiguille d'Abrams —A propos de 1000 prèlévements. Interet de la biopsie pleuroscopique. Poumon 1975; 31:317-323

44. American Thoracic Society—Statement by the Committee on Therapy, Gryzbowski S (Chairman): Therapy of pleural effusion. Am Rev Respir Dis 1968; 97:479-483

45. Berger HW, Mejia E: Tuberculous pleurisy. Chest 1973; 63:88-92

46. Race G, Scheifey C, Edwards J: Hydrothorax in congestive heart failure. Am J Med 1957; 22:83-90

47. Light RW: Diseases of the pleura, In Tice F (Ed): Practice of Medicine, Vol 5. Hagerstown, MD, WF Prior Co, 1963, p 23

48. Luce SA, Reagan JW: A histocytological study of effusions —I. Effusions not associated with malignant tumors. Cancer 1954; 7:1155-1166

49. Pillay VK: Total protein in serous fluids in cardiac failure. South Afr Med J 1965; 39:142-143

50. Lieberman FL, Hidemaura R, Peters RL, et al: Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. Ann Intern Med 1966; 64:431-451

51. Taryle DA, Sahn SA: The incidence and clinical correlates of parapneumonic effusions in pneumonoccal pneumonia. Chest 1978; 74:170-173

52. Light RW, Girard WM, Jenkinson SF, et al: Parapneumonic effusions. Am J Med 1980; 69:507-512

53. Fine NL, Smith LR, Sheedy PF: Frequency of pleural effusion in mycoplasma and viral pneumonias. N Engl J Med 1970; 283:790-793

54. Bartlett JG, Gorbach SL, Thadepalli H, et al: Bacteriology of empyema. Lancet 1974; 1:388-340

55. Meyer PC: Metastatic carcinoma of the pleura. Thorax 1966; 21:437-443

56. Cernow B, Sahn SA: Carcinomatous involvement of the pleura—An analysis of 96 patients. Am J Med 1977; 63:695-702

57. Maher GG, Berger HW: Massive pleural effusion: Malignant and nonmalignant causes in 46 patients. Am Rev Respir Dis 1972; 105:458-460

58. Sahn SA: Pleural effusion in lung cancer, *In* Matthay RA (Ed): Clinical Chest Medicine—Vol 3, Lung Cancer: Recent Advances. Philadelphia, WB Saunders, 1982, pp 443-452

59. Spriggs AI, Boddington MM: Absence of mesothelial cells from tuberculous pleural effusions. Thorax 1960; 15:169-171

60. Walker WC, Wright V: Rheumatoid pleuritis. Ann Rheum Dis 1967; 26:467-474

61. Carr DT, Mayne JG: Pleurisy with effusion in rheumatoid arthritis with reference to the low concentration of glucose in pleural fluid. Am Rev Respir Dis 1962; 85:345-350

62. Sahn SA, Kaplan RL, Maulitz RM, et al: Rheumatoid pleurisy: Observations on the development of low pleural fluid pH and glucose. Arch Intern Med 1980; 140:1237-1238

63. Dodson WH, Hollingsworth JW: Pleural effusion in rheumatoid arthritis: Impaired transport of glucose. N Engl J Med 1966; 275:1337-1342

64. Kaye M: Pleuropulmonary complications of pancreatitis. Thorax 1968; 23:297-306

65. Taryle DA, Good JT Jr, Morgan E, et al: Antibiotic penetration into human parapneumonic effusions. J Antimicrobial Chemo 1981; 7:171-177

66. Sahn SA, Good JT Jr, Potts DE: The pH of sclerosing agents: A determinant of pleural symphysis. Chest 1979; 76:198-200